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IV FLUIDMAKER III. TEST AND EVALUATION OF 1 L/HR PROTOTYPE

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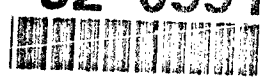

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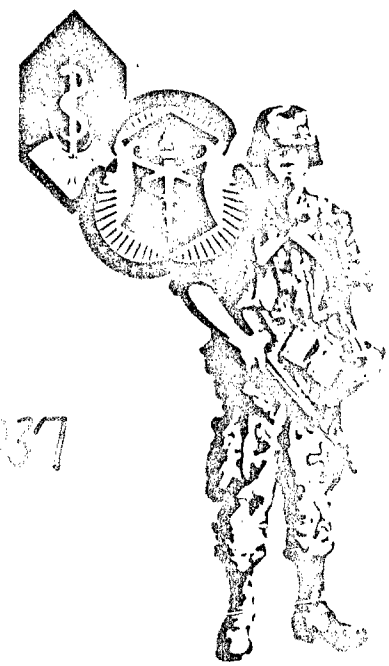

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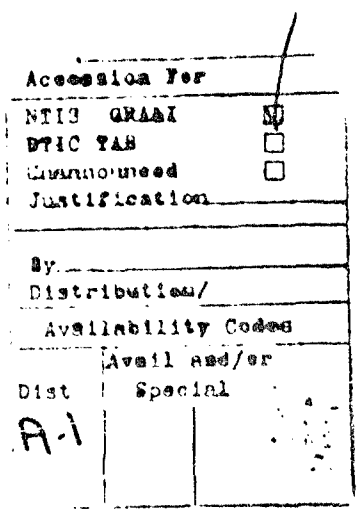

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Hand-operated fluidmakers capable of producing 1 L/hr of water for injection have been tested for their ability to remove endotoxins, oxidizables, chloride and bacteria from a challenge water having high levels of all measured parameters. Three fluidmakers consisted of a reverse osmosis unit, an ion exchange column, a water purification filter and a sterilizing filter in series; two others were identical except for the lack of ion exchange columns. Three fluidmakers failed before 50 L of product water was collected, probably because of excessive back pressure resulting from clogged sterilizing filters. A number of samples of product water exhibited endotoxin contamination, and several were not sterile. All samples were out of limit for chloride ion, and 10 percent were out of limit for oxidizables. A sixth fluidmaker (without an ion exchange column) was operated for 50 L by means of a mechanical cycling machine. Sterilizing filters were changed after every liter of product water, the reverse osmosis unit functioned normally, and the product water was sterile and nonpyrogenic.

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PREFACE

Chemical analyses were performed under the direction of Dr. Steven H. Hoke, U.S. Army Biomedical Research and Development Laboratory (USABRDL). Endotoxin tests for the manually operated fluidmaker were conducted by Ms. Kathleen Connor of PRI, Inc. Sterile water tests for the fluidmaker were carried out under the direction of Ms. Linda Spaetz, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The USABRDL acknowledges with gratitude the assistance of the following Medical Research Volunteers from USAMRIID: PFC John West, SPC Paul Gilson, PFC Grant Wright and SPC Peter Tebo.

INTRODUCTION

The U.S. Army Medical Research and Development Command requires a device to manufacture intravenous (IV) fluids in adverse circumstances, such as a field combat situation, where resupply of medical items is uncertain.[1] The device must produce sterile, pyrogen-free water which can be introduced directly into sterile bags with sterile salt solution to make one liter of Ringer's lactate or one liter of 5 percent dextrose in water suitable for IV infusion into humans. Approval by the Food and Drug Administration is ultimately required but not considered to be a part of this study. Operational requirements for the device are:

a. It must be hand-operated.

b. It must produce at least one liter of fluid per hour.

c. The supply water must be taken from a potable source.

d. It should fit into a protective mask container (ca. 20 cm X 23 cm X 8 cm).

In a previous study, two systems were devised for generating sterile, pyrogen-free water for injection (WFI) and were shown capable of producing WFI according to U.S. Pharmacopeia (USP) standards while meeting the other design requirements presented above.[2] Both systems utilized reverse osmosis (RO), ion exchange, a solid matrix filter containing activated carbon and zeta adsorbent, a final 0.2 μm pore-size sterilizing filter and a device for transferring the WFI to an IV bag. The smaller of the two weighed approximately 1.5 kg and produced one liter of WFI in 45-60 minutes. The larger unit weighed approximately 3.5 kg, produced one liter of WFI in 5-6 minutes, but somewhat exceeded the size requirement.

This report presents results and conclusions from tests designed to evaluate the performance of the smaller unit described above under simulated military field conditions and to identify problems to be corrected. Test results for the larger unit have been reported elsewhere.[3]

APPROACH AND RATIONALE

General performance requirements for the fluidmaker in terms of product quality are that it reduce dissolved inorganic and organic chemicals, including pyrogens (endotoxins), to very low levels; that it virtually eliminate residual suspended materials; and that it assure sterile transfer to an IV bag. The target for the device in question (hereinafter the fluidmaker) is Sterile Water for Injection as defined by the USPXXII.[4] The USP manufacturing and purity criteria for Sterile Water for Injection are presented in Appendix A.

The system is designed to function as follows: chlorine-free supply water is treated by reverse osmosis, which reduces all common ions and heavy metals

by 98 percent or greater and effectively removes most dissolved organic impurities and all microorganisms, including viruses. Next, a mixed-bed ion exchange column reduces dissolved salts to levels acceptable for WFI. A water purification filter containing activated carbon then is used to trap organic chemicals missed by RO and to remove pathogens and pyrogens. A membrane filter of 0.2 μm limiting pore size follows the water purification filter to ensure sterility, and the product WFI is transferred to an IV bag. Except as noted below, system components were identical to those described in the original study[2].

Because USABRDL resources were insufficient to perform the entire battery of tests required by USPXXII, it was decided to limit these tests to the following: endotoxins, sterility, total chloride, pH and oxidizable substances. Limited heavy metal analyses were also performed.

MATERIALS AND METHODS

REVERSE OSMOSIS. The Survivor™ 06 hand-operated RO unit, manufactured by Recovery Engineering, Inc., Minneapolis, MN, was used for all tests. Connections between the various units used in these tests were made with Tygon® tubing of appropriate size.

ION EXCHANGE COLUMN. The smallest ion exchange (IE) columns available off-the-shelf were purchased from Vaponics, Inc., Plymouth, MA (Cat. No. MRN-254F). Ten inches long, the IE columns were packed with strong acid - strong base, mixed bed ion exchange resin and were fitted with end cap nipples. These units were much larger than necessary for a field usable device, but were used because of their availability. These IE columns followed the RO units on three of five fluidmakers. Inlet and outlet nipples were fitted with Luer-Lok® connectors.

WATER PURIFICATION FILTER. The First Need® water purification filter (General Ecology, Inc., Lionville, PA) used throughout this study is a solid matrix filter containing activated carbon and zeta adsorbents; it is rated at 0.1 μm nominal and 0.4 μm absolute. It is a cylinder 7 cm in diameter, ca. 10 cm long, weighs 0.20 kg, and produces 400 to 500 mL/min at the maximum pumping rate recommended by the manufacturer. Void volume is 20 to 30 mL. Inlet and outlet nipples were fitted with Luer-Lok® connectors.

STERILIZING FILTER. A Nalgene presterilized 50 mm syringe filter with 0.2 μm pore-size cellulose acetate membrane (Nalge Company, Rochester, NY) was attached to the outlet of the First Need® filter and was replaced as indicated (Appendix C). Product water was collected directly from the end of the sterilizing filter, without the benefit of a sterile transfer procedure. This collection procedure was necessitated by the unavailability of enough sterile transfer sets, as used in the original study.[2]

SAMPLING AND TESTING PROCEDURE. Two test series were performed. For the first series, five fluidmakers, comprising the above unit treatment processes, were operated manually. Challenge water (450 gal.) was prepared by amending Fort Detrick tap water with sodium chloride and t-butyl alcohol. Free

chlorine (which would have damaged the RO membranes) was removed from the water by stirring for several days. The t-butyl alcohol was added in three aliquots of 170 g (100 mg/L) each on February 5, 12 and 20, i.e., the beginning of each work week. Analyses of challenge water are presented in Appendix B. By the end of the test period, the supply water was visibly dirty and contaminated with algae. Samples were collected for each liter of product water according to the schedule in Appendix C and analyzed for endotoxins, chloride ion, oxidizables, and sterility. First Need[R] filters and sterilizing filters were replaced at the beginning of each work day and after work breaks. Sterilizing filters were also replaced when reduced product flow and visual evidence indicated fouling.

For the second series, a single fluidmaker without an ion exchange unit was operated at a rate of 1 L/hr by means of a mechanical cycling machine, which drove the RO unit at 90 strokes/min. Challenge water (50 gal.) was prepared by adding 824 mg/L of sodium chloride (500 mg/L as chloride ion) to Fort Detrick tapwater, providing a total dissolved solids content of ca. 1000 mg/L. This water was allowed to stand for two weeks before testing to remove free chlorine and to allow the bacteria concentration to build up. Samples were collected for each two liters of product and analyzed for endotoxins, conductivity and sterility according to the schedule in Appendix C. A new First Need[R] filter (flushed with 1 L of tapwater to remove loose particulate matter) and a freshly sterilized product tube joining the First Need[R] filter to the sterilizing filter were put into service at the beginning of each work day. Sterilizing filters were replaced after collection of each liter of product water.

ANALYTICAL PROCEDURES. Product water (3-5 mL) was collected by free catch from the sterilizing filter. Pyrogen (endotoxins) content was determined using the Limulus amebocyte lysate chromogenic assay (Pyrogent Plus, Whittaker Bioproducts, Inc., Walkersville, MD). The detection limit was 0.06 endotoxin units (eu) per mL. Bacterial testing was conducted using BBL[R] prepared media (Becton Dickinson Microbiological Systems, Cockeysville, MD). Custom ordered split media plates were used; one side of the plate consisted of TSA II[R] (Trypticase[R] soy agar with 5 percent Sheep Blood) and the other side contained MacConkey agar (MAC). A sample volume of 0.2 ml/side/plate was used for inoculations. Chloride ion concentration was determined by ion chromatography; the detection limit was lower than that specified by USPXXII. Oxidizable substances were determined by the USP procedure (Appendix A). The detection limit for t-butyl alcohol was 60 mg/L.

RESULTS AND DISCUSSION

The research plan called for fifty 1.0 L samples of product water to be collected from each of five fluidmakers. However, three of five RO units failed before 50 L could be collected, as evidenced by reduced product flow and leaking. Inspection of the failed units by the manufacturer revealed that ring seals had been displaced due to excessive back pressure. This problem resulted from plugging of the sterilizing filters by particulate matter from the First Need[R] filters, as noted earlier.[3]

Analytical results are summarized in Table 1. Performance was generally unsatisfactory, in marked contrast to the larger systems.[3] Two of five fluidmaker systems produced occasional nonsterile samples, and four of five gave frequent samples exhibiting endotoxin contamination. Endotoxin contamination most probably resulted from microbial colonization of the Tygon[R] tube joining the First Need[R] filter and sterilization filter as previously observed;[2] the sterilizing filter removes bacteria, but not endotoxins. Nonsterile samples most likely resulted from nonspecific postcollection contamination; this would be eliminated by the use a sterile transfer set, as in the original fluidmaker study.[2]

TABLE 1. SUMMARY OF TEST RESULTS

Fluidmaker No.	Sterility total[a]	Sterility o/l[b]	Endotoxins total[a]	Endotoxins o/l[b]	Oxidizables total[a]	Oxidizables o/l[b]	Chloride total[a]	Chloride o/l[b]
1 (IE)[c]	30	0	30	0	30	1	30	30
2 (IE)[c]	50	0	50	7	49	3	49	49
3 (IE)[c]	46	0	46	17	46	5	45	45
4	50	6	47	30	50	8	50	50
5	4	2	4	2	4	0	49	49
6[d]	25[e]	0	25[e]	0				

a. Total number of 1.0 L samples
b. o/l = out of limit
c. These fluidmakers included an ion exchange (IE) column.
d. This unit was mechanically operated.
e. 2.0 L samples

Ten percent of the samples were out of limit with respect to USPXXII standards for oxidizable substances. Although the percent of samples containing oxidizable substances is about the same as observed for the larger systems,[3] the incidence in this study was random and did not regularly follow installation of a new First Need[R] filter. As with the larger system,[3] chloride ion levels in product water were out of limit whether or not an ion exchange column was installed. The chloride level of the challenge water matched that to be expected for potable water produced by the Army's reverse osmosis water purification unit (ROWPU) when drawing its supply from seawater. These results indicate that a better ion exchange unit will be needed to meet the chloride standard of USPXXII. This Laboratory is presently developing such a device under contract.

Because the larger system reliably produced sterile, pyrogen-free water (but not USPXXII WFI), and because the two systems differ only in capacity of the RO units, it was decided to perform a second series of tests with the

Survivor™ 06 system under more carefully controlled conditions. To that end, a sixth device was assembled and driven by a mechanical cycling machine rather than by manpower. A new First Need® filter was installed at the beginning of each day's run, and the tube joining the First Need® and sterilizing filters was disinfected. Sterilizing filters were replaced after each liter of product water, and samples were collected for every two liters. Although the bacterial and endotoxin challenge levels far exceeded that of any likely potable source, no growth was detected for any sample on either sheep's blood agar or MacConkey agar, and endotoxin levels were below the detection limit for all samples (fluidmaker no. 6, Table 1). These tests, in agreement with the original study,[2] indicate that the smaller fluidmaker can reliably produce sterile, pyrogen free water, provided that sterilizing filters are changed frequently. This should not present a problem in actual field use, since it will probably be recommended that the sterilizing filter be part of the transfer set and be replaced with each liter of product. Conductivity of the product water, measured as a surrogate for chloride ion, was reduced by 98±1 percent (which is within the range expected for RO), but still exceeded the limit for USPXXII WFI.

CONCLUSIONS AND RECOMMENDATIONS

1. The 1 L/hr fluidmaker tested can reliably produce sterile, pyrogen-free water from microbiologically contaminated potable water provided that the sterilizing filter can be prevented from plugging and generating unacceptable back pressure in the RO unit. Otherwise, conclusions and recommendations are the same as for the 6 L/hr fluidmaker.[3]

2. Further testing is needed to establish whether this device can meet the limit for oxidizable substances of USPXXII from a realistic challenge water. For this purpose, only the First Need® filter requires testing.

3. An ion exchange unit specifically designed for this system is needed. No further action is required at this time, since contracts to address this problem are in effect.

4. It may be necessary to develop a small, inline prefilter (depth filter) to protect the final sterilizing filter from fine particulates shed by the First Need® filter.

LITERATURE CITED

1. Memorandum, US Army Medical Research and Development Command, SGRD-PLB, 21 April 1988, subject: IV Fluidmaker.

2. Burrows, W.D. and J.H. Nelson. 1988. IV fluidmaker: Preparation of sterile water for injection in a field setting. Technical Report 8814, AD A207411. Frederick, MD: U.S. Army Biomedical Research and Development Laboratory.

3. Rogers, T.L., Jr., W.D. Burrows and J.H. Nelson. 1990. IV fluidmaker II. Testing and evaluation of 6 L/hr prototype. Technical Report 9008, AD A235816. Frederick, MD: U.S. Army Biomedical Research and Development Laboratory.

4. United States Pharmacopeial Convention. 1990. The United States Pharmacopeia, Twenty-Second Revision. Rockville, MD: United States Pharmacopeial Convention, Inc.

APPENDIX A: STERILE WATER FOR INJECTION[4]

Sterile Water for Injection is Water for Injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Packaging and storage -- Preserve in single-dose containers, preferably of Type I or Type II glass, of not larger than 1-liter size.
Labeling -- Label it to indicate that no antimicrobial or other substance has been added, and that it is not suitable for intravascular injection without its first having been made appropriately isotonic by the addition of a suitable solute.
Reference standard -- USP Endotoxin Reference Standard.
Bacterial endotoxins -- When tested as directed under Bacterial Endotoxins Test <85>, the USP Endotoxin RS being used, it contains not more than 0.25 USP Endotoxin Unit per mL.
Sterility -- It meets the requirements under Sterility Tests <71>.
Ammonia -- For Sterile Water for Injection in glass containers holding a volume up to 50 mL, dilute 50 mL with 50 mL of High-purity Water (see Reagents under Containers <661>), and use this dilution as the test solution; where larger volumes are held, use 100 mL of Sterile Water for Injection as the test solution. To 100 mL of the test solution add 2 mL of mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in High-purity Water (see Reagents under Containers <661>)(0.6 ppm for Sterile Water for Injection packaged in volumes up to 50 mL in containers; 0.3 ppm for larger volumes).
Chloride -- To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of High-purity Water (see under Reagents in Containers <661>) containing 10 µg of Cl (0.5 ppm), viewed downward over a dark surface with light entering the tubes from the sides.
Oxidizable substances -- To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Injection in containers holding a volume up to 50 mL, add 0.4 mL of 0.1 N potassium permanganate, and boil for 5 minutes; for larger volumes, add 0.2 mL of 0.1 N potassium permanganate, and boil for 5 minutes: the pink color does not completely disappear.
Total solids -- Proceed as directed in the test for Total solids under Purified Water. The following limits apply for Sterile Water for Injection in glass containers holding up to 30 mL, 0.004%; from 30 mL up to 100 mL, 0.003%; and for larger volumes, 0.002%.
Other requirements -- It meets the requirements of the tests for pH, Sulfate, Calcium, Carbon dioxide, and Heavy metals under Purified Water.

APPENDIX B: TEST WATER SUPPLY ANALYSES

Date	Pyrogen eu/mL[a]	Sterility cfu/mL[b]	Chloride mg/L	Oxidizables mg/L[c]	pH
02-05-90	18	3,000	577	>100	7
02-06-90	55.4	>100,000	541	>100	7
02-07-90	169.7	>100,000	531	>100	7
02-08-90	508.5	>100,000	646	>100	7
02-09-90	161.3	>100,000	591	>100	6
02-12-90	466.1	>100,000	684	>100	7
02-13-90	743.6	>100,000	587	>100	7
02-14-90	554.3	>100,000	542	>100	7
02-15-90	270	>100,000	558	>100	7
02-16-90	893.3	>100,000	549	>100	7
02-20-90	1,128.3	75,000	544	>100	7
02-21-90	900	d	567	>100	7
02-22-90	864.1	>100,000	602	>100	7
02-23-90	93.7	50,000	500	>100	7
02-26-90	295.0	35,000	589	>100	7
02-27-90	288.5	>100,000	513	>100	8
02-28-90	435.7	100,000	519	>100	6
03-01-90	1053.8	>100,000	524	>100	7
03-02-90	499.8	>100,000	508	>100	7

a. Endotoxin units/mL
b. Colony-forming units/mL
c. As t-butyl alcohol
d. Limited growth on either MacConkey's agar or sheep's blood agar

APPENDIX C: TEST RESULTS

TABLE C1. TEST UNIT NO. 1: WITH ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
02-06-90	1128	new	new	<0.06	0	1.163	-
	1133			<0.06	0	1.225	-
	1138			<0.06	0	1.337	-
	1143			<0.06	0	1.158	-
02-07-90	1148	new	new	<0.06	0	8.571	-
	1153			<0.06	0	3.682	-
	1159		new	<0.06	0	2.120	-
02-08-90	1164	new	new	<0.06	0	7.561	-
	1169			<0.06	0	2.835	-
	1174			<0.06	0	1.974	-
	1179			<0.06	0	1.563	-
	1184			<0.06	0	1.386	-
02-09-90	1190	new	new	<0.06	0	6.927	-
	1195			<0.06	0	2.679	-
	1200			<0.06	0	1.688	-
	1205		new	<0.06	0	1.268	-
02-12-90	1210	new	new	<0.06	0	4.327	-
	1215			<0.06	0	1.550	-
	1221			<0.06	0	1.501	-
	1226			<0.06	0	1.199	-
02-13-90	1231	new	new	<0.06	0	8.345	+
	1236			<0.06	0	3.301	-
	1241			<0.06	0	1.601	-
	1246			<0.06	0	1.236	-
02-14-90	1251	new	new	<0.06	0	8.105	-
	1383	new	new	<0.06	0	0.872	-
02-21-90	1388	new	new	<0.06	0	8.642	-
	1393			<0.06	0	3.355	-
	1398			<0.06	0	2.081	-
	1403[c]			67.9	0	1.876	-

a. Endotoxin units
b. Colony forming units; 0 = no growth in 48 hours
c. Test series terminated because of unit failure

TABLE C2. TEST UNIT NO. 2: WITH ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
02-07-90	1129	new	new	0.12	0	12.503	-
	1134			0.21	0	5.296	+
02-08-90	1139	new	new	<0.06	0	8.983	-
	1144			<0.06	0	4.531	-
	1149			<0.06	0		
	1154			<0.06	0	3.074	-
	1160			<0.06	0	2.407	-
	1165			<0.06	0	2.173	-
02-09-90	1170	new	new	0.08	0	9.490	-
	1175			<0.06	0	3.858	-
	1180			<0.06	0	2.801	-
	1185		new	<0.06	0	2.457	-
	1191			<0.06	0	2.187	-
02-12-90	1196	new	new	<0.06	0	7.330	-
	1201			<0.06	0	3.127	-
	1206			<0.06	0	1.967	-
	1211			<0.06	0	1.520	-
	1216			<0.06	0	1.952	-
02-13-90	1222	new	new	0.07	0	6.459	-
	1227		new	<0.06	0	3.033	-
	1232			<0.06	0	2.212	-
	1237			<0.06	0	1.798	+
02-14-90	1242	new	new	<0.06	0	9.005	-
	1247			<0.06	0	3.946	-
	1252		new	<0.06	0	2.952	-
	1384	new	new	0.07	0	2.843	+
02-21-90	1389	new	new	0.23	0	13.200	-
	1394			<0.06	0	3.673	-
	1399			<0.06	0	2.684	-
	1404			<0.06	0	2.470	-
02-22-90	1409	new	new	0.13	0	11.564	-
	1415			49.0	0	5.291	-
	1420			1.27	0	3.719	-
	1425			<0.06	0	2.997	-
02-23-90	1430	new	new	0.17	0	21.983	-
	1435			142.2	0	7.962	-
	1440			66.1	0	5.194	-
	1446			<0.06	0	4.231	-
	1451			<0.06	0	3.318	
02-26-90	1456	new	new	2.00	0	17.369	-
	1461			3.60	0	7.052	-
	1466			8.40	0	3.026	-
	1471			0.19	0	3.848	-
	1477			0.12	0	3.161	-
	1482			0.12	0	3.061	-

TABLE C2, CONT. TEST UNIT NO. 2: WITH ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
02-27-90	1487	new	new	59.52	0	9.361	-
	1492			63.3	0	2.950	-
	1497			92.7	0	3.666	-
	1502			44.1	0	1.418	-
	1507			43.5	0	2.924	-

a. Endotoxin units
b. Colony forming units; 0 = no growth in 48 hours

TABLE C3. TEST UNIT NO. 3: WITH ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
02-07-90	1130	new	new	<0.06	0	9.299	+
	1135			<0.06	0	2.889	-
	1140			<0.06	0	8.192	+
02-08-90	1145	new	new	<0.06	0	8.765	-
	1150			<0.06	0		
	1155			<0.06	0	3.245	-
	1161			<0.06	0	2.181	-
02-09-90	1166	new	new	<0.06	0	7.844	-
	1171		new	<0.06	0	2.599	-
	1176			<0.06	0	1.396	-
02-12-90	1181	new	new	<0.06	0	7.210	-
	1186			<0.06	0	3.115	-
	1192			<0.06	0	1.992	-
	1197			<0.06	0	1.467	-
02-13-90	1202	new	new	<0.06	0	6.758	-
	1207		new	<0.06	0	3.141	-
	1212			<0.06	0	2.041	-
02-14-90	1217	new	new	<0.06	0	6.901	-
	1223			<0.06	0	2.937	-
02-15-90	1228	new	new	59.3	0	5.729	-
	1233			31.4	0	2.535	-
	1238			26.0	0	1.591	-
02-16-90	1243	new	new	<0.06	0	8.459	-
02-20-90	1248	new	new	0.14	0	8.442	-
	1253			1.46	0	4.809	-
	1385		new	<0.06	0	2.375	-
02-21-90	1390	new	new	0.47	0	10.026	-
	1395			0.11	0	2.517	-

TABLE C3, CONT. TEST UNIT NO. 3: WITH ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
	1400			0.23	0	2.195	-
02-22-90	1405	new	new	2.20	0	10.137	-
	1410			0.46	0	6.226	-
	1416			104.6	0	2.912	-
02-23-90	1421	new	new	0.43	0	8.540	-
	1426			0.69	0	5.085	-
	1431			<0.06	0	1.323	-
02-26-90	1436	new	new	117.7	0	10.587	-
	1441		new	81.1	0	5.603	-
	1447			39.8	0	2.848	+
	1452			30.8	0	2.022	-
02-28-90	1457[c]	new	new		0	16.354	+
	1462[c]				0	5.123	-
	1467[c]				0	5.336	-
	1472[c]		new		0	3.213	+
03-01-90	1478	new	new	0.80	0	8.684	-
	1483			1.10	0	5.542	-
	1488[d]			24.2	0	4.392	-

a. Endotoxin units
b. Colony forming units; 0 = no growth in 48 hours.
c. Sample not tested for pyrogen
d. Test series terminated because of unit failure

TABLE C4. TEST UNIT NO. 4: WITHOUT ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
02-06-90	1131	new	new	<0.06	0	4.311	+
	1136			<0.06	0	3.497	-
	1141			<0.06	0	4.329	-
	1146			<0.06	0	3.476	-
02-07-90	1151	new	new	<0.06	0	9.658	+
	1156			<0.06	0	3.551	-
02-09-90	1162	new	new	1.00	0	7.171	-
	1167			0.14	0	4.009	-
	1172			0.07	0	2.407	-
02-12-90	1177	new	new	0.12	0	24.382	+
	1182			<0.06	0	6.506	-
	1187			<0.06	0	3.939	-
	1193			<0.06	0	3.215	-

TABLE C4, CONT. TEST UNIT NO. 4: WITHOUT ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
02-13-90	1198	new	new	1.04	1	12.212	+
	1203		new	0.76	0	5.498	-
	1208			21.8	1	3.810	-
02-14-90	1213	new	new	7.6	0	6.023	-
	1218		new	<0.06	0	3.154	-
	1224			<0.06	0	15.657	-
02-15-90	1229	new	new	2.2	0	8.222	-
	1234			0.28	0	9.433	+
	1239			79.9	0	105.4	+
02-16-90	1244	new	new	4.18	0	13.18	-
	1249			0.28	0	7.144	-
	1254			0.17	0	2.619	-
	1386	new	new	0.38	0	3.023	-
	1391			0.67	0	1.772	-
02-23-90	1396	new	new	1.66	0	10.368	-
	1401		new	39.1	0	8.198	+
	1406		new	0.24	0	2.744	-
02-26-90	1411	new	new	3.2	0	11.994	-
	1417			1.9	0	4.298	-
	1422		new	42.7	0	1.493	-
	1427			52.9	0	1.841	-
	1432			57.8	5	59.635	+
02-28-90	1437[c]	new	new		0	15.534	+
	1442[c]				0	8.933	+
	1448		new	225.7	2	5.719	+
	1453[c]				0	4.343	-
03-01-90	1458	new	new	96.9	0	9.397	-
	1463			345.8	0	5.536	-
	1468			0.19	0	3.392	-
	1473			73.1	0	7.075	-
	1479			148.0	10	3.485	-
	1484			83.6	0	2.427	-
	1489			22.6	2	3.145	-
03-02-90	1494	new	new	3.1	0	14.018	-
	1499			2.4	0	4.843	-
	1504			40.2	0	8.538	-
	1509			8.4	0	6.405	-

a. Endotoxin units
b. Colony forming units; 0 = no growth in 48 hours.
c. Sample not tested for pyrogen

TABLE C5. TEST UNIT NO. 5: WITHOUT ION EXCHANGE COLUMN

Date	Sample	Filters		Pyrogen	Sterility	Chloride	Oxidiz.
		carbon	steril.	eu/mL[a]	cfu/mL[b]	mg/L	
02-07-90	1132	new	new	<0.06	0	3.014	+
02-08-90	1137	new	new	0.99	0	10.874	+
	1142		new	0.90	0	3.292	-
	1147[c]			<0.06	0	2.072	-

a. Endotoxin units
b. Colony forming units; 0 = no growth in 48 hours.
c. Test series terminated because of unit failure

TABLE C6. TEST UNIT NO. 6: MECHANICALLY OPERATED

Date	Sample	Filters		Pyrogen	Sterility	Conductivity
		carbon	steril.[a]	eu/mL[b]	cfu/mL[c]	μmho/cm
10-31-90	Feed			≥60	29,000	1500
	2 L	new	new	<0.06	0	30
	4 L		new	<0.06	0	
	6 L		new	<0.06	0	22
	8 L		new	<0.06	0	
11-01-90	Feed			≥60	41,000	1700
	10 L	new	new	<0.06	0	24
	12 L		new	<0.06	0	
	14 L		new	<0.06	0	20
	16 L		new	<0.06	0	18
11-02-90	Feed			≥60	22,500	
	18 L	new	new	<0.06	0	
	20 L		new	<0.06	0	
	22 L		new	<0.06	0	
	24 L		new	<0.06	0	
11-03-90	Feed			≥60	22,100	1600
	26 L	new	new	<0.06	0	17
	28 L		new	<0.06	0	
	30 L		new	<0.06	0	
11-05-90	Feed			≥60	21,100	1700
	32 L	new	new	<0.06	0	48
	34 L		new	<0.06	0	26
	36 L		new	<0.06	0	
	38 L		new	<0.06	0	18
11-06-90	Feed			≥60		1800
	40 L	new	new	<0.06	0	35
	42 L		new	<0.06	0	25
	44 L		new	<0.06	0	
	46 L		new	<0.06	0	
11-07-90	Feed			≥60		1800
	48 L	new	new	<0.06	0	45
	50 L		new	<0.06	0	21

a. Sterilizing filter changed ca. every liter of product.
b. Endotoxin units
c. Colony forming units; 0 = no growth in 48 hours.

APPENDIX D

GLOSSARY OF TERMS

cfu	colony forming units
eu	endotoxin units
IE	ion exchange
IV	intravenous
RO	reverse osmosis
ROWPU	Reverse Osmosis Water Purification Unit
USABRDL	U.S. Army Biomedical Research and Development Laboratory
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USP	U.S. Pharmacopeia
USPXXII	U.S. Pharmacopeia, Twenty-Second Revision

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